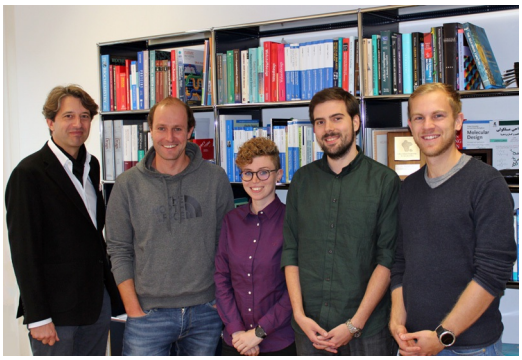
Discovery of Novel Molecular Frameworks of Farnesoid X Receptor Modulators by Ensemble Machine Learning



From left to right: G. Schneider, D. Merk, F. Grisoni, K. Schaller, L. Friedrich.

Invited for this month's cover picture is the group of Prof. Dr. Gisbert Schneider from the Swiss Federal Institute of Technology (ETH) Zurich (Switzerland). The cover picture illustrates the application of machine-learning methods to expand the chemical space of farnesoid X receptor (FXR)-targeting small molecules, by employing an ensemble of three complementary machine-learning approaches (counter-propagation artificial neural network, k-nearest neighbor learner, and three-dimensional pharmacophore model). Read the full text of their Full Paper at 10.1002/open.201800156.

What is the most significant result of this study?

In this work, we developed and experimentally validated an ensemble machine-learning strategy to identify novel molecular frameworks of FXR modulators. A prospective virtual screening on a library of 3 million compounds allowed us to identify novel FXR activator and antagonist frameworks, which expand the chemical space of known FXR modulators. This study demonstrates the potential of ensemble machine learning for prospective hit finding and to capture pharmacologically relevant features of known bioactives without the need of previous structure–activity knowledge.

Who designed the cover?

The cover was designed by Dr. Francesca Grisoni.

What prompted you to investigate this topic/problem?

Machine learning holds particular potential in computer-assisted hit discovery. To streamline hit identification from large compound collections, we have employed an ensemble of complementary machine-learning methods to capture different aspects of the dataset and improve the prediction quality. FXR was chosen as the molecular target for its great therapeutic potential and the limited diversity of known FXR ligand frameworks. As potent FXR agonists advancing to, or in, clinical trials are represented by few chemotypes, we have employed our computational approach to FXR ligand identification to equip medicinal chemistry with fresh lead compounds for FXR targeted drug discovery.

What other topics are you working on at the moment?

We are focusing on artificial intelligence (AI)-driven de novo molecular design and have employed neural networks to learn the "grammar" of SMILES strings and, subsequently, generate new chemical entities (NCEs). By means of transfer learning, this model can be tailored to specific applications such as target-focused or natural-product-inspired de novo design. In prospective applications, AI-designed molecules were synthesized and confirmed as bioactive. We are now further expanding and improving the application of generative AI for the de novo design of innovative NCEs.

Acknowledgements

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